Exhibit C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA
FT. LAUDERDALE DIVISION

CASE NO.: 18-CV-61047

UNITED STATES OF AMERICA,

Plaintiff,

v.

US STEM CELL CLINIC, LLC, a Florida limited liability company,
US STEM CELL, INC., a Florida profit corporation, and
KRISTIN C. COMELLA and THEODORE GRADEL, individuals,

Defendants.

Rebuttal Expert Report of Elliot B. Lander, M.D., FASC

I. QUALIFICATIONS

I am a Board Certified Urologist and Co-Medical Director of Cell Surgical Network ("CSN"), a translational research organization dedicated to the investigation of autologous stromal vascular fraction ("SVF"). I graduated *magna cum laude* and Phi Beta Kappa from Occidental College in 1982 with Distinction in Biochemistry, after which I attended medical school at the University of California, Irvine from 1982-1986. Following medical school, I continued to study General Surgery and then Urologic Surgery at University of California Irvine, where, from 1992 to 1997, I was on staff as a Clinical Assistant Professor of Urology. During this same timeframe, I was also in practice as a partner physician at the Kaiser Permanente Medical Group.[1]

I have been elected as a Fellow of the American College of Surgeons. I also served as Chief of Urology at Eisenhower Medical Center in Rancho Mirage, California, and Chief of Surgery at John F. Kennedy Hospital in Indio, California. I have been on staff at Eisenhower Medical Center for twenty years, and also act as an Expert Reviewer in Urology for the California Medical Board. In addition to my current role as Co-Founder and Co-Medical Director of CSN, I continue to perform clinical research on liposome encapsulated agents for the treatment of interstitial cystitis.

With respect to my work with stem cells, I helped develop a simple surgical method of SVF procurement that has been used by CSN since 2010. This SVF procurement procedure is

[1] *See* Curriculum Vitae, Elliot B. Lander, M.D., FASC attached hereto at **Attachment 1**.

currently deployed under ten active International Review Board ("IRB") investigational protocols, which I wrote along with my partner, Mark Berman, M.D., FASC. Currently, over 10,000 patients are registered in the database.

I have written extensively on SVF and various applications of autologous SVF procedures, including several articles published in peer reviewed journals. I lecture regularly around the world on SVF science, teach physicians to use SVF safely and effectively, and peer review regenerative medicine publications for several journals.[2]

II. STATEMENT OF OPINIONS

Given my scientific expertise and medical experience and expertise, I have been asked to review and respond to Expert Reports submitted by the Government in this matter. In connection with this work, I reviewed various materials, including information referenced in the Government's Experts' Reports, as well as materials related to the surgical procedure performed by US Stem Cell Clinic, LLC ("USSCC") that involves the procurement of the patient's own SVF for relocation into another area of the patient's body ("SVF Procedure"). My review encompassed an evaluation of documentation detailing the surgical techniques used in USSCC's SVF Procedure, including the surgical protocol.[3] Further, I carefully reviewed the scientific literature, including human clinical study data, to evaluate the safety and effectiveness of USSCC's SVF Procedure. Finally, I considered the techniques and outcome measures of USSCC's SVF Procedure relative to other surgical procedures involving human stem cells to assess the safety and efficacy of the SVF Procedure compared to other commonly-performed surgical procedures involving stem cells.

Based on my review of this information, and for the reasons discussed below, I believe with a reasonable degree of medical certainty that, contrary to the opinions of the Government's Experts: (1) the patient's SVF cells that are collected in the performance of USSCC's SVF Procedure do not undergo any changes before those same SVF cells are subsequently relocated back into the patient's body; and (2) the use of SVF in surgical procedures is safe and well-tolerated.

A. <u>USSCC's SVF Procedure is a Surgery involving the Patient's Unique SVF Cells</u>

USSCC's SVF Procedure is a medical service that involves the relocation of a patient's own SVF during a single outpatient surgical procedure, performed at a USSCC clinic by a licensed healthcare professional ("HCP"). As suggested by its name, a "stromal vascular fraction" is a fraction – or part of – adipose tissue. Specifically, SVF is comprised entirely of a population of various stromal and vascular cells derived from the patient's adipose tissue, including adipose stem cells (also known as "mesenchymal stem cells"), hematopoietic stem cells, pericytes, endothelial/progenitor cells, white blood cells, and fibroblasts. Obtaining these SVF cells merely requires separating the stromal and vascular cell populations (*i.e.*, "fractions") from the adipocyte (fat) cell population ("fraction") of the patient's adipose tissue.

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[2] *Id.*
[3] *See* US Stem Cell Clinic, LCC, A Step-by-Step Guide, attached hereto as **Attachment 2**.

USSCC's SVF Procedure is designed to provide a regenerative effect to the patient's body using the stromal and vascular cells' innate biological function to heal and repair tissue. Indeed, as discussed in detail in Section II.B below, the stromal and vascular cells in adipose tissue have profound regenerative properties.[4]

To collect the patient's SVF cells, the HCP uses "tumescent liposuction" of the patient's adipose tissue. Next, the unwanted adipocyte fraction is separated from the desired SVF (stromal and vascular fractions) using routine surgical tools—namely, collagenase and a FDA 510(k)-cleared centrifuge device. As described below, the collagenase breaks down the collagen strands that hold the adipocyte, stromal and vascular cells together in the adipose tissue—it does not, however, break down or otherwise impact any of these cells.[5] Finally, the SVF is suspended in a sterile saline solution so that the SVF can be relocated back into the patient's body in a specific area of need. In short, USSCC offers a medical service to its patients that has the effect of assisting in the body's natural ability to repair itself.

Importantly, the abovementioned surgical techniques employed by USSCC involve relocation of the very same SVF cell population that *previously existed* in the patient's body, not the creation or manufacture of any new "product" for introduction into the body. This is in stark contrast to FDA-regulated drug/biologic products, such as CAR-T therapies, that rely on collection of a patient's cells, addition of a novel gene therapy in a laboratory, and subsequent growth of the new product (*i.e.*, stem cells + gene addition) for transplant back into the patient.[6] USSCC's SVF Procedure, in contrast, does not involve adding any novel gene therapies to a patient's cells.

Rather, in the case of USSCC's SVF Procedure, the stromal and vascular cells taken out of the patient in the performance of the procedure are the same cells that are put back into the patient. As explained in Section II.B below, the SVF cells are non-engineered (*i.e.*, not changed) but merely collected from the patient's body using surgical tools in the operating room (not a laboratory) to separate them from the adipose tissue.

Moreover, unlike manufactured drugs, the SVF Procedure does not require USSCC to produce any cellular- or tissue-based product to uniform specifications for strength, quality and purity. While safety and efficacy considerations require that drug products be manufactured in a uniform manner for use in various patients, uniform processing is not necessary (nor for that matter feasible) with the SVF Procedure. Rather, the cell population used in the SVF Procedure is unique to each patient, including the specific stem cell count. The outcomes of the SVF Procedure are also uniquely based on the patient's own tissue and cannot be replicated across patients. And, unlike drug products which are provided based on an established effective dose, the patient's own

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[4] *See* Section II.B *infra* pages 4-8 (providing a detailed discussion of the regenerative properties of the stromal and vascular cell population contained in adipose tissue); *see also* Kershaw EE & Flier JS. *Adipose tissue as an endocrine organ.* J Clin Endocrinol Metab. 2004 Jun; 89(6):2548-56 (hereinafter cited as "Kershaw Paper" attached hereto as **Attachment 3**); Coelho M et al. *Biochemistry of adipose tissue: an endocrine organ*. Arch Med Sci. 2013; 9, 2: 191-200, at 191 (hereinafter cited as "Coelho Paper" attached hereto as **Attachment 4**).

[5] *See* Section II.B *infra* pages 4-8 (noting that collagenase does not affect any stromal, vascular, or adipocyte cells).

[6] For example, CAR-T therapies involve extraction of patient's T-cells and subsequent addition in a laboratory of a novel special receptor gene (*i.e.*, chimeric antigen receptor (CAR)) introduced by a virus into the T-cells to create an entirely new biologic product—one that had not previously existed in the patient's body. Large numbers of the CAR T-cells are grown in the laboratory and, ultimately, this novel, patentable, biologic product is given to the patient via infusion.

stem cells function to effect repair of damaged tissues in the body.[7] The *only* feature SVF shares with traditional FDA-regulated biologic drug products, such as CAR-T therapies, is that the stromal and vascular fractions are from a live source.

B. <u>USSCC's SVF Procedure Does Not Alter the Characteristics of the Patient's SVF Cells</u>

i. USSCC Uses Surgical Tools to Collect and Relocate the Patients Preexisting SVF cells

Dr. Yong suggested in her Expert Report that the SVF extracted by USSCC in performance of the procedure undergoes significant processing, however that is not the case. Instead, based on my review of USSCC's surgical protocols, USSCC simply extracts the patient's SVF cells, and uses limited surgical tools to remove the unwanted remains of the adipose tissue (*i.e.*, adipocyte fraction) before relocating the same SVF cell population back into the same patient.

As an initial matter, it is the SVF contained in the patient's adipose tissue that USSCC's SVF Procedure targets for collection from the patient, as the stromal and vascular fractions contain the patient's regenerative cells to heal the body.[8] Indeed, as explained in a 2018 study by Kilinc et al., of which I am also an author, "[a]dipose-derived stem cells ["ADSC"] have regenerative potential and exhibit anti-inflammatory, immunomodulatory, and pro-angiogenic effects [and] [b]ecause of these distinctive characteristics, SVF, which includes ADSC, holds a great promise in regenerative medicine . . ."[9] For that reason, the relevant cell population at issue in USSCC's SVF Procedure is the SVF.

The patient's SVF is collected via tumescent liposuction of the adipose tissue, after which USSCC cleans and separates the SVF from the unwanted adipocyte fraction (*i.e.*, waste) using the surgical tools of collagenase and centrifugation. More specifically, collagenase is used in the SVF Procedure to help eliminate unnecessary adipocytes waste that surround the SVF. Importantly, the collagenase enzyme effects *only* the collagen matrix of the adipose tissue that holds the three cell fractions of adipose (stromal, vascular, and adipocyte (fat) cells) together.[10] The collagenase does not, however, break or digest any cells.[11] Further, and critically, the collagenase does not

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[7] *See, e.g.*, Gimble JM, Katz AJ, Bunnell BA. *Adipose-derived stem cells for regenerative medicine*. Circ Res. 2007;100:1249-1260; Bellows CF, Zhang Y, Chen J, Frazier ML, Kolonin MG. *Circulation of progenitor cells in obese and lean colorectal cancer patients*. Cancer Epidemiology Biomarkers & Prevention. 2011;20:2461-2468; Bellows CF, Zhang Y, Simmons PJ, Khalsa AS, Kolonin MG. *Influence of bmi on level of circulating progenitor cells. Obesity*. 2011; 19: 1722-1726.

[8] *See, e.g.*, Kilinc MO et al. *The ratio of ADSCs to HSC-progenitors in adipose tissue derived SVF may provide the key to predict the outcome of stem-cell therapy*. Clin Transl Med. 2018, 7: 5 (hereinafter cited as "Kilinc Paper" attached hereto as **Attachment 5**); Hematti P & Keating A (2013) *Mesenchymal stromal cells in regenerative medicine: a perspective. Mesenchymal stromal cells: biology and clinical applications*. Human Press, New York; Kokai LE, Marra K, Rubin JP (2014) *Adipose stem cells: biology and clinical applications for tissue repair and regeneration*. Transl Res 63:399–408.

[9] Kilinc Paper, **Attachment 5** at 2.

[10] *See, e.g.*, Autengruber A et al. *Impact of enzymatic tissue disintegration on the level of surface molecule expression and immune cell function*. Eur J Microbiol and Immunol, 2, pp. 112-120 (2012) (noting that, unlike dispase, collagenase does not have any significant effects on tissue disintegration).

[11] *See* Sakaguchi Y et al. *Suspended cells from trabecular bone by collagenase digestion become virtually identical to mesenchymal stem cells obtained from marrow aspirates*. Blood J Org., 2004 104: 2728-2735 (noting that "suspended

present any residual toxicity or damage to the SVF cells[12] and is removed prior to subsequent relocation of the SVF back into the patient.[13]

Likewise, USSCC's use of an FDA 510(k)-cleared centrifuge helps clean and size the SVF so that only the desired SVF component is available for relocation back into the patient. Notably, centrifugation is used in numerous surgical procedures, including bone marrow aspirate for regenerative purposes, where the device's effect in separating cells and tissue does not subject these procedures to FDA regulation.[14] Similarly, in USSCC's SVF Procedure, the centrifuge tool helps ensure that the small part of the organ (*i.e.*, the SVF) is available for relocation back into the patient's body during the SVF Procedure. The centrifugation process does not result in anything being added back into the patient that was not already existing in the patient's body.

Finally, it is critical to note that the surgical tools used by USSCC to wash and separate the SVF cells from the adipocyte cell fraction do not change the physical form of the SVF cells. The stromal and vascular cells remain unchanged from their original liquid cellular form. Similarly, the adipocyte cell fraction (the remaining fat) is unchanged from its original foamy structural form, but is discarded as waste after separation from the stromal and vascular cell fractions. USSCC's surgical techniques do not convert any adipose fraction from structural to liquid, rather, it is the process of removing excess adipocyte debris that leaves behind a liquid cellular SVF component (essentially identical to bone marrow aspirate) that is replete with regenerative properties.[15]

ii. The Original Regenerative Characteristics of the Patient's SVF Cells Do Not Change

Dr. Yong takes the position that the original structural characteristics of cushioning and support of adipose tissue are changed through the performance of USSCC's SVF Procedure.[16] This conclusion, however, is an inaccurate over simplification of the cellular make up of adipose tissue and the regenerative characteristics of the SVF contained in adipose. Dr. Yong recognizes that SVF contained in adipose tissue is comprised of various cell types including pre-adipocytes and vascular endothelial cells—both of which are stem cells—and also admits that adipose tissue has multiple functions including regenerative functions.[17] Yet, her Expert Report fails to properly consider the functions of adipose tissue and the cells that comprise it. Those functions include

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cells from trabecular bone by collagenase digestion were virtually identical to mesenchymal stem cells obtained from marrow aspirates").

[12] *See* Chang H et al. *Safety of adipose-derived stem cells and collagenase in fat tissue preparation*. Aesthetic Plast Surg. 2013 Aug; 37(4):802-8 ("no toxicity resulting from residual collagenase or tumorigenicity associated with the ADSCs [adipose derived stem cells] was observed").

[13] Confirmation that collagenase is washed out (*i.e.*, removed) from the SVF is evidenced by simple assay. *See*, e.g., Berman M & Lander E. *A prospective safety study of autologous adipose-derived stromal vascular fraction using a specialized surgical processing system*. American J of Cosmetic Surg. 2017:1–14, at 8-9 (hereinafter cited as "Safety Study" attached hereto as **Attachment 6)**.

[14] FDA has indicated that use of a centrifuge to remove debris from the desired cells or tissue does not constitute processing that would subject cells or tissue to regulation as a drug. *See* FDA Guidance, *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception* (Nov. 2017).

[15] Autologous bone marrow aspirate for regenerative purposes is used routinely in surgery without FDA regulation as a drug product.

[16] *See* Export Report of Carolyn Yong, Ph.D., dated December 21, 2018, at 4, 9-10 (hereinafter cited as "Yong Report").

[17] *See* Yong Report at 6.

regenerative tissue repair and healing, insulation, metabolic properties and energy storage, and complex endocrine properties.

For example, as explained by Coelho, adipose tissue "is no longer considered to be an inert tissue that stores fat . . . [t]his dynamic tissue is composed not only of adipocytes, but also of other cell types called the stroma-vascular fraction, comprising blood cells, endothelial cells, pericytes and adipose precursor cells among others."[18] Likewise, Kershaw emphasizes that "adipose tissue is a complex, essential, and highly active metabolic and endocrine organ. . . [that] not only responds to afferent signals from traditional hormone systems and the central nervous system but also expresses and secretes factors with important endocrine functions."[19] In fact, adipose has endocrine properties to such an advanced degree that The Endocrine Society[20] considers fat to be an "endocrine organ" as opposed to a simple fat storage organ that was traditionally understood.[21] As also explained by Kershaw, "adipose tissue is integrally involved in coordinating a variety of biological processes including energy metabolism, neuroendocrine function, and immune function."[22]

Importantly, adipose has the highest number of regenerative cells of any tissue in the body by weight.[23] While Dr. Yong's report includes images of adipose tissue via electron micrograph,[24] these images are outdated as electron micrograph technology does not show the most critical regenerative cells.[25] As explained in a publication by Birbrair, "until recently, light and electron microscopy were the only techniques able to visualize [pericytes] and pericytes distinct from vascular smooth muscle cells. . . perivascular fibroblasts, juxtavascular microglia and other perivascular cells could not be identified precisely."[26] Through the use of updated photo imaging techniques, the structure of adipose tissue is now understood as a complex combination of (1) stromal connective tissue with pre-adipocytes (progenitor stem cells); (2) adipocytes (fat cells); and (3) a complex vascular network that includes the very important pericyte cells which represent mesenchymal stem cells.[27] There is a significant amount of published literature devoted to the

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[18] Coelho Paper, **Attachment 4.**

[19] Kershaw Paper, **Attachment 3**; *see also* Coelho Paper, **Attachment 4**.

[20] The Endocrine Society has 18,000 members and serves "as the primary professional home for endocrine scientists and clinical practitioners." *See About the Endocrine Society* (last visited Jan. 21 2019), *available at* https://www.endocrine.org/about-us.

[21] *See* Kershaw Paper, **Attachment 3**.

[22] *Id.* at 191.

[23] *See* Mizuno H & Hyakusoku H. *Fat grafting to the breast and adipose-derived stem cells: recent scientific consensus and controversy*. Aesthet Surg J. 2010 May-Jun;30 (3):381-7 at 385 (noting that "studies have shown that 1 g of adipose tissue yields approximately 5 x 10^8 stem cells, which is 100 – 500 times greater than the number of mesenchymal stem cells (MSC) in 1 g of bone marrow"); *see also* Kitigawa Y et al. *History of discovery of human adipose-derived stem cells and their clinical application*. Jpn. J Plast Reconstr Surg 2006; 49; 1097-1104.; Fraser JK, Wulur I, Alfonso Z, Hendrick MH. *Fat tissue; an underappreciated source of stem cells for biotechnology*. Trends Biotechnol 2006:24:150-154.

[24] *See* Yong Report at 5.

[25] *See, e.g.*, Birbrair A et al. *Pericytes at the intersection between tissue regeneration and pathology*. Clin Sci (Lond). 2015 Jan 1; 128(2): 81–93.

[26] Birbrair A et al. *Pericytes at the intersection between tissue regeneration and pathology*. Clin Sci (Lond). 2015; 128(2): 81–93.

[27] *See* Photos of Adipose Tissue from Lipogems Co. attached hereto as **Exhibit 1**. Indeed, there are hundreds of publications discussing the role of pericytes as stem cells. *See, e.g.*, Birbrair A et al. *Role of pericytes in skeletal muscle regeneration and fat accumulation*. Stem Cells Dev. 2013 Aug 15; 22(16): 2298–2314; Hardy WR et al. *Transcriptional networks in single perivascular cells sorted from human adipose tissue reveal a hierarchy of*

various stem cells found in adipose tissue, and particularly the connective tissue in adipose tissue, especially the blood vessels (pericytes) intimately branching through the tissue.[28]

Because of its stem cell composition, adipose tissue contains cells that have multiple purposes critical for the development of new blood vessels, more fat, cartilage, muscle, nerves, and other subcutaneous tissues. The widespread healing system in adipose tissue is important for repair of the body that suffers injury, trauma, and disease. Fat also surrounds vital organs and supports healing in this manner. Most of the important mesenchymal stem cells come from vascular fractions, which include the pericytes that are found along blood vessels and also the endothelial progenitors found inside blood vessels.[29] Stem cells are also found around fat globules (the stromal fraction).

There is abundant literature dedicated to these important regenerative cells and the properties of adipose due to the SVF cell population. For example, adipose contains stem cells capable of repairing and regenerating damaged tissues such as irradiated skin, alleviating fibrotic changes, improving mobility and vitality, and repairing structures such as hair follicles and lymphatics.[30] The adipose stem cells also serve as progenitors of cells which contribute to the vascular network formation and vascular structures.[31] Importantly, the adipose stem cells serve a role shared by stem cells located in nearly all body tissues, including bone marrow, and their vascular functions serve a homologous regenerative function to that already present in the adipose tissue.[32] Indeed, omental fat is called the "policeman of the abdomen"[33] and medical students are taught in basic general surgery that the omental fat accelerates healing. A general surgeon wraps omental fat around a surgical bowel anastomosis to accelerate healing and prevent infection (not as a cushion).

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mesenchymal stem cells. Stem Cells. 2017 May; 35(5):1273-1289; Hindle P et al. *The infrapatellar fat pad as a source of perivascular stem cells with increased chondrogenic potential for regenerative medicine*. Stem Cells Transl Med. 2017 Jan; 6(1):77-87; Kim EJ et al. *Platelet-derived growth factor receptor-positive pericytic cells of white adipose tissue from critical limb ischemia patients display mesenchymal stem cell-like properties*. Clin Orthop Surg. 2017 Jun; 9(2):239-248.

[28] *See id.*

[29] *See id.*

[30] *See, e.g.*, Gimble JM, Katz AJ, Bunnell BA. *Adipose-derived stem cells for regenerative medicine*. Circ Res. 2007; 100:1249-1260; Bellows CF, Zhang Y, Chen J, Frazier ML, Kolonin MG. *Circulation of progenitor cells in obese and lean colorectal cancer patients*. Cancer Epidemiol Biomarkers Prev. 2011; 20:2461-2468; Bellows CF, Zhang Y, Simmons PJ, Khalsa AS, Kolonin MG. *Influence of bmi on level of circulating progenitor cells*. Obesity. 2011; 19:1722-1726.

[31] *See, e.g.*, Traktuev DO et al. *A population of multipotent CD34-positive adipose stromal cells share pericyte and mesenchymal surface markers, reside in a periendothelial location, and stabilize endothelial networks*. Circ Res. 2008; 102:77-85; Traktuev DO et al. *Robust functional vascular network formation in vivo by cooperation of adipose progenitor and endothelial cells*. Circ Res. 2009; 104:1410-1420; Merfeld-Clauss S, Gollahalli N, March KL, Traktuev DO. *Adipose tissue progenitor cells directly interact with endothelial cells to induce vascular network formation*. Tissue Eng Part A. 2010; 16:2953-2966; Merfeld-Clauss S et al. *Adipose stromal cells differentiate along a smooth muscle lineage pathway upon endothelial cell contact via induction of activin A*. Circ Res. 2014; 115:800-809.

[32] *See, e.g.*, Crisan M et al. *A perivascular origin for mesenchymal stem cells in multiple human organs*. Cell stem cell. 2008; 3:301-313.

[33] *See, e.g.*, Liebermann-Meffert D. *The greater omentum: anatomy, embryology, and surgical applications*. Surg Clin North Am. 2000 Feb; 80(1):275-93.

In short, regeneration and repair (rather than cushioning) may be one of the most important functions of adipose and likely why there are 100-1000 times more repair cells (stem cells) found in adipose tissue than in an equivalent volume of bone marrow. SVF maintains these natural properties of the adipose tissue that were always present and always intended for the purpose of repair.

In light of the above, I believe to a reasonable degree of medical certainty that the SVF that is injected back into the patient during USSCC's SVF procedure contains the same cells that were extracted from the patient's body, and those SVF cells continue to perform their innate function of healing and repair in the body as they did prior to USSCC's SVF Procedure.

C. The Use of SVF in Surgical Procedures is Safe and Well-Tolerated

i. Scientific Literature Demonstrates the Safety of Autologous SVF

An evaluation of the scientific literature reveals that autologous use of SVF surgical procedures have a robust safety profile. For example, in a review of over 1000 human clinical trials on stem cells, the authors found no publications suggesting evidence of patient harm associated with autologous stem cell treatment for regeneration.[34] Additional confirmation of safety with respect to autologous treatment with mesenchymal stem cell transplants, including those used in the performance of SVF surgical procedures, is evidenced in numerous publications throughout the scientific literature.[35] For example, as stated in a 2015 study by Michalek evaluating the safety and efficacy of SVF in patients:

> [T]here is strong previously documented clinical evidence of safety of autologous non-manipulated or minimally manipulated cell therapies. In the first decade of the 21st century, more than 17,000 scientific articles involving 2,724 cell therapy clinical trials were published. These results include 323,000 patients treated with more than 675,000 cell therapy units. The treatments were very safe and often very effective in the treatment of various diseases with the potential to significantly improve health worldwide.[36]

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[34] Van Pham P. *Clinical trials for stem cell transplantation: when are they needed?* Stem Cell Res Ther. 2016; 7:65.
[35] *See, e.g.*, Michalek J et al. *Autologous adipose tissue-derived stromal vascular fraction cells application in patients with osteoarthritis: a case control prospective multi-centric non-randomized study*. Glob Surg, 2017; 3(3): 1-9 (hereinafter cited as "Michalek Study" attached hereto as **Attachment 7**); Guo J et al. *Stromal vascular fraction: a regenerative reality? Part 2: mechanisms of regenerative action*. J Plast Reconstr Aesthet Surg. 2016; 69(2):180-188; Nguyen A, Guo J, Banyard DA, et al. *Stromal vascular fraction: a regenerative reality? Part 1: current concepts and review of the literature.* J Plast Reconstr Aesthet Surg. 2016; 69(2):170-179; Benoit E, O'Donnell TF, Patel AN. *Safety and efficacy of autologous cell therapy in critical limb ischemia: a systematic review*. Cell Transplant. 2013; 22(3):545-562; Ma XR et al. *Transplantation of autologous mesenchymal stem cells for end-stage liver cirrhosis: a meta-analysis based on seven controlled trials.* Gastroenterol Res Pract. 2015; Sun X, Ying J, Wang Y, et al. *Meta-analysis on autologous stem cell transplantation in the treatment of limb ischemic*. Int J Clin Exp Med. 2015;8(6):8740-8748; Van Pham P. *Clinical trials for stem cell transplantation: when are they needed?* Stem Cell Res Ther. 2016;7:6; *autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes mellitus: a randomized placebo-controlled study*. Cell Transplant. 2014;23(9):1075-1085; Kilinc OM et al. *The ratio of ADSCs to HSC-progenitors in adipose tissue derived SVF may provide the key to predict the outcome of stem-cell therapy,* Clin Trans Med. 2018; 7:5.
[36] Michalek Paper, **Attachment 7** at 8).

The scientific literature is consistent with my 2017 published prospective safety study evaluating 1698 autologous use SVF procedures performed between 2011 and 2016 ("Safety Study").[37] More specifically, the Safety Study analyzed adverse events associated with SVF procedures to evaluate safety as a primary objective and secondarily efficacy of SVF deployed through intra-articular injections and intravenous infusions for a variety of orthopedic and non-orthopedic conditions. Importantly, the study focused on SVF procedures that used similar methods and protocols as USSCC's SVF Procedure. The Safety Study data revealed (i) a very low number of reported adverse events following the SVF procedures and (ii) a reduction in pain ratings after 6 months or more across a variety of musculoskeletal diseases and improvements in a variety of other degenerative conditions. For example, in response to a patient-reported questionnaire regarding the occurrence of adverse events attributed by the patient, 515 respondents (98.1%) answered with "no."[38] Similarly, the rate of any severe reaction to the SVF procedure was reported by patients at extremely low numbers, 0.1% - 2.0% of respondents, and such responses were primarily related to pain during the liposuction portion of the SVF procedure.[39] Importantly, no severe infections, allergic reactions, pulmonary embolic, or deep vein thromboses were reported following the SVF procedures.

These robust findings of the Safety Study are in line with animal studies on SVF therapy. Indeed, SVF has been extensively used as a regenerative therapy in animals, particularly dogs and racehorses, with excellent safety and efficacy.[40] For example, numerous veterinary patients have received intra-articular autologous SVF to mitigate arthritis and orthopedic injuries successfully.[41] Finally, it should be noted that CSN now has a 10,000 patient database that tracks safety and efficacy of SVF procedures, and to date, the reports of any concerns regarding the SVF procedures are extremely low.

Based on my review of the scientific literature and my involvement in a prospective safety analysis of SVF procedures using the same techniques as USSCC's, I conclude that USSCC's SVF Procedure is safe for patients.

ii. Dr. Lapteva's Safety Assessment is Not Supported by the Science

While Dr. Larissa Lapteva's evaluation of the safety of USSCC's SVF Procedure attempts to raise doubt as to the safety of USSCC's SVF Procedure,[42] her conclusions are not supported by a detailed review of the scientific literature and are not medically accurate. As an initial matter, in evaluating the scientific literature to assess the safety and efficacy of the SVF Procedure, Dr. Lapteva omitted two of the most robust publications in the world on the use of SVF in human orthopedics—the 2017 Safety Study[43] and the 2017 Michalek Study,[44] each of which found no

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[37] *See* Safety Study at **Attachment 6**.
[38] *Id.* at 8.
[39] *Id.*
[40] *See, e.g.*, Black LL, Gaynor J, Gahring D, et al. *Effect of adipose-derived mesenchymal stem and regenerative cells on lameness in dogs with chronic osteoarthritis of the coxofemoral joints: a randomized, double-blinded, multicenter, controlled trial*. Vet Ther. 2007; 8(4):272-284.
[41] *Id.*
[42] *See* Export Report of Larissa Lapteva, M.D., dated December 21, 2018.
[43] *See* Safety Study, **Attachment 6**.
[44] *See* Michalek Study, **Attachment 7**.

evidence of safety concerns with SVF procedures. The failure to consider these peer-reviewed publications calls into question the rigor of Dr. Lapteva's review.

Additionally, Dr. Lapteva's analysis of potential toxicity concerns is not medically accurate. More specifically, while Dr. Lapteva attempts to suggest that USSCC's SVF Procedure could present potential risks of pulmonary embolism, Dr. Lapteva's conclusion is not well founded because it relies on studies of cultured mesenchymal stem cells ("MSC"), not SVF. For example, Dr. Lapteva's evaluation of the Jung study involved a family with a familial hypercoagulability (prone to pulmonary embolism) problem in Korea, and the stem cells they received were cultured stem cells, not SVF. For this reason, the findings of the Jung study cannot be relied upon to analyze the safety of USSCC's SVF Procedure. Dr. Lapteva's evaluation of a second study, Tatsumi, likewise refers to a patient who had stem cell transplantation and had a fatal PE; again however, that patient received cultured MSC and not SVF.[45] The authors of that publication also noted that the pro-coagulant activity in the sample was only present in cultured cells, while the fresh uncultured adipose derived cells (similar to SVF) they evaluated did not have this problem.[46] Accordingly, this publication is not relevant. Additional articles cited by Dr. Lapteva likewise involved treatments unrelated to SVF deployment.[47]

MSC cell therapy and SVF deployment are entirely different cell therapy treatments and should not be confused with each other. For example, MSC cells are occasionally autologous but mostly allogeneic (*i.e.*, from another person), whereas SVF is nearly always autologous, as is the case with USSCC's SVF Procedure. Further, MSC cell lines are cultured in a laboratory to represent a single lineage of cells, while SVF has four different types of stem cells[48] in a unique number per individual. Finally, not all MSCs are the same: MSC lines contain MSC cells that are grown in culture broth containing growth factors and may have different biochemical and histologic (microscopic appearance) characteristics compared to the fresh progenitor MSC cells identified as one of the components of SVF.

For these reasons, studies using MSC lines for cell therapy cannot be used to evaluate the safety of SVF Procedures. Indeed, I am not aware of any cases in the world of pulmonary embolism due to an SVF Procedure. There have been tens of thousands of patients who have had SVF Procedures and the incidence of pulmonary embolism with routine abdominal surgery is 0.64%, suggesting that SVF may in fact be protective against pulmonary embolism.

Dr. Lapteva also makes reference to alleged serious neurological complications based on her finding that one SVF procedure patient had elevated CSF fluid protein and multiple medical problems with urinary tract infection. There is absolutely no evidence, however, that this was

[45] *See* Tatsume K et al. *Tissue factor triggers procoagulation in transplanted mesenchysmal stem cells leading to thromboembolism*. Biochem Biophys Res Commun. 2013; 431(2) 203-209.
[46] *Id*.
[47] *See, e.g.*, Lalu MM et al. *Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials*. PLoS One. 2012; 7(10) (retrospective review of MSC injections); Staff NP et al. Safety of intrathecal autologous adipose-derived mesenchymal stromal cells in patients with ALS. Neurology. 2016 Nov; 87(21) 2230-2234 (expanded MSC therapy); Hur JW et al. Intrathecal transplantation of autologous adipose-derived mesenchymal stem cells for treating spinal cord injury: A human trial. J Spinal Cord Med. 2016 Nov; 39(6) 655-664 (expanded MSC cells).
[48] The four types are: MSC, pericytes, endothelial progenitor, and hematopoietic stem cells. *See* Kilinc Paper, **Attachment 5**.

related to treatment with SVF deployment. Further, her discussion of the Pak publication regarding tendonitis effects involved a patient that received SVF mixed with platelet rich plasma—comingling therapies may cause potential side effects. Accordingly, it is inaccurate for Dr. Lapteva to jump to the conclusion that SVF treatment would cause or raise the risk of these medical concerns. Finally, her discussion of possible retina detachment is not supported by the scientific literature, and the exact etiology of the retina detachments is yet to be adjudicated and elucidated.

In short, Dr. Lapteva has not shown any cause and effect or given a medical or physiologic reason as to why or how SVF would have caused any of the serious complications she described in her Export Report. Indeed, most of the toxicity reports cited by Dr. Lapteva involved treatments other than SVF, and certain publications in fact support the safety of SVF. In light of my evaluation of Dr. Lapteva's report, I find that the conclusions reached by Dr. Lapteva as to the safety of USSCC's Procedure are not grounded in an accurate or robust review of the scientific literature.

iii. Robust Safe Surgical Practices Help Ensure Patients' Safety

The absence of safety concerns attributable to SVF procedures, including USSCC's SVF Procedure, is not surprising based on my evaluation of the medical standards and state regulatory requirements that are in place to help ensure patient safety. While the SVF Procedure is not performed in accordance with the good manufacturing practices (GMP) requirements applicable to mass produced drug products, there are nevertheless numerous protocols and precautions in place to ensure the patients' safety.

For example, as a board certified surgeon, I can attest to the rigor of various state medical board requirements to which surgeon's must adhere in order to prioritize patient safety. Additionally, accepted safe surgical practices for SVF development are published in the scientific literature to help provide guidance as to the safety of surgical techniques for this procedure. In fact, I routinely help train surgeons in the safe performance of SVF procedures.

With respect to USSCC's SVF Procedure, the procedure is performed under proper surgical conditions. Further, USSCC's SVF Procedure is subject to regulation by the Florida Board of Osteopathic Medicine which classifies various "levels" of office surgery[49] and for which the Florida Department of Health has established administrative rules governing the standard of care, requirements for training and equipment, and standards for anesthesia and liposuction procedures.[50] Florida statutes also reflect standards and other requirements relating to the practice of osteopathic medicine.[51] Finally, medical literature contains information useful to stem cell therapy clinics with respect to appropriate processing controls for stem cell therapy transplants.

In short, based on my review of the scientific literature, including my evaluating of the studies presented in Dr. Lapteva's Expert Report, as well as the surgical processes and procedures

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[49] *See* Florida Board of Medicine "What are the Different Levels of Surgery" *available at* http://flboardofmedicine.gov/help-center/what-are-the-different-levels-of-surgery/.

[50] *See* Florida Dept. of Health, Board of Medicine, Rule 64B8-9.009, *Standard of Care for Office Surgery available at* https://www.flrules.org/gateway/ruleNo.asp?id=64B8-9.009.

[51] *See* 32 Fla. Statutes § 459.01 et seq.

followed by USSCC in the performance of the SVF Procedure, I conclude that USSCC's SVF Procedure is overall safe for patients and well-tolerated.

III. CONCLUSION

Based on the information that I have reviewed, I believe that, to a reasonable degree of medical certainty, USSCC's SVF Procedure is a safe surgical procedure, and one that simply involves relocation of a patient's own SVF from one location in a patient's body to another, without any change in the physical or biological characteristics of those SVF cells.

IV. ATTACHMENTS

Attachment 1: Curriculum vitae

Attachment 2: US Stem Cell Clinic, A Step-by-Step Guide

Attachment 3: Kershaw Paper 2004

Attachment 4: Coelho Paper 2013

Attachment 5: Kilinc Paper 2018

Attachment 6: Safety Study 2017

Attachment 7: Michalek Study 2017

V. EXHIBITS USED TO SUPPORT OPINION

Exhibit 1: Photos of Adipose Tissue Lipogems Co.

VI. MATERIALS REVIEWED

1. Materials related to USSCC's surgical protocols.
2. Other materials, including but not limited to scientific literature, as cited or referenced in this Report.
3. The Government's Export Reports:
    a. Expert Report of Larissa Lapteva, M.D. dated December 21, 2018, and materials referenced therein.
    b. Expert Report of Carolyn Yong, Ph.D. dated December 21, 2018, and materials referenced therein.
    c. Export Report of Randa F. Melhem, Ph.D. dated December 21, 2018, and materials referenced therein.

VII. OTHER AREAS OF POSSIBLE TESTIMONY

I may offer testimony on topics, within my field of expertise and which are not currently known, but may be adduced at or before trial as the evidence develops. I will also be prepared to offer additional rebuttal testimony. This testimony will be dependent on an evaluation of the testimony on similar topics offered by a witness called by the opposing party.

VIII. COMPENSATION

None.

IX. PRIOR EXPERT TESTIMONY

I have not testified by deposition or at trial in any case in the last four years.

X. PUBLICATIONS

Lander E, Berman M. Autologous Stromal Vascular Fraction: A New Era of Personal Cell Therapy. J Stem Cell Res Dev Ther 2018 4:011.

Lander E, Berman, M. Autologous Stromal Vascular Fraction Containing Stem Cells Combined with Low Intensity Shock Wave for the Treatment of Human Erectile Dysfunction. J Stem Cell Res Ther 2018, 8:9.

Berman S, Uhlendorf T, Berman M, Lander EB. Effective Treatment of Traumatic Brain Injury in Rowett Nude Rats with Stromal Vascular Fraction Transplantation. Brain Sci 2018, 8, 112.

Manuscript accepted for publication: Draganov et al. Lander E. "Delivery of Oncolytic Vaccinia Virus by Matched Allogeneic Stem Cells Overcomes Critical Innate and Adaptive Immune Barriers" Journal of Translational Medicine Feb 27th 2018.

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Berman S, Uhlendorf TL, Mills DK, Lander EB, Berman MH, Cohen RW. Validation of Acoustic Wave Induced Traumatic Brain Injury in Rats. Brain Sci. 2017 Jun 2;7(6).

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DeHaan FP, Delker G, Covey W, Bellomo A, Brown J, Ferrara D, Haubrich R, Lander EB, MacArthur C. Electrophilic Aromatic Substitution. 6. A Kinetic Study of the Formylation of Aromatics with 1, 1-Dichloromethyl Methyl Ether in Nitromethane. *J. Org. Chem.*, 1984, 49 (21), pp 3963–3966

Detection of Unsuspected cognitive impairment in Cardiac rehabilitation patients. Chapter 24 in "Post Myocardial Infraction Management and Rehabilitation.'' M. Dekker, Inc, 1983.

Study of Salivary and Serum Antibody Response in Mice following oral challenge with S. Mutans. Winning paper at California statewide NASA Youth Science Congress. Los Angeles, California. 1978.

Book Author:

Co-author of "The Stem Cell Revolution." By Mark Berman MD and Elliot Lander MD. 2015 Authorhouse Company

Authored "Forward" in "Desmystifying Stem Cells- A Real Life Approach." By Bohdan Olesnicky MD and Naota Hashimoto DC.

XI. SUPPLEMENTATION

I reserve the right to supplement this report or my testimony.

Dated: January 22, 2019

Respectfully submitted,

Elliot B. Lander, MD, FACS
Board Certified Urologist
Co-Founder and Co-Medical Director, Cell Surgical Network